Association between Genetic Polymorphism rs2952768, Close to the METTL21A and CREB1 Genes, and Intellectual Ability in Healthy Subjects

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Abstract

Objective: Human intelligence, which represents a set of cognitive abilities, is assumed to be a highly heterogenic trait. The Intelligence Quotient (IQ) is the most widely used index for characterizing human intelligence in psychometric studies, and knowledge of the genes associated with IQ has continuously grown. Several previous reports indicated that IQ may be associated with addictive behaviors or the use of addictive substances, although the trend toward an association is not straightforward and depends on the substances abused. To explore the genetic factors that contribute to IQ, we conducted an association study of a genetic polymorphism, rs2952768. The rs2952768 single-nucleotide polymorphism (SNP) was recently reported to be associated with human opioid sensitivity and shown to be associated with the efficacy of opioid analgesics, severity of substance dependence, and mRNA expression levels of a neighboring gene, CREB1.

Methods: The present study used data from 298 biologically unrelated Japanese subjects. Psychiatrically, medically, and neurologically healthy subjects were evaluated using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Non-Patient Edition (SCID-I/NP), to exclude individuals who had substance-related disorders, who had received psychiatric medications, or who had first- or second-degree relatives with psychiatric disorders. Genotyping was performed using the Affymetrix Genome-Wide Human SNP Array 6.0. The rs2952768 SNP close to the METTL21A gene was extracted from this dataset. Multiple linear regression analysis was performed to compare intellectual ability among rs2952768 SNP genotypes.

Results: A significant effect of the SNP genotype was observed on current IQ ($\beta = -2.27, p = 0.026$). The number of non-risk major C allele for drug and alcohol dependence was correlated with higher IQ scores.

Conclusion: The present results suggest that the rs2952768 SNP, which was identified as a potent SNP associated with human opioid sensitivity, is also one of the genetic factors that contribute to human intellectual ability.

Keywords: Intelligence Quotient (IQ); Opioids; Addictive substances; Substance dependence; Single-nucleotide polymorphism (SNP); Cyclic adenosine monophosphate response element binding protein 1 (CREB1); Methyltransferase like 21A (METTL21A)

Introduction

Human intelligence, which represents a set of cognitive abilities, such as thinking, remembering, reading, learning, problem solving, and using language, is assumed to be a highly heterogenic trait. Intelligence Quotient (IQ) is the most widely used index for characterizing human intelligence in psychometric studies. It can be used to assess intellectual ability in not only healthy subjects but also in patients with disorders such as schizophrenia, autism, depression, and anxiety [1–3]. Among the well-examined genes are those involved in brain functions related to mechanisms of learning and memory, and genetic variations in such genes associated with IQ have been identified [4–6]. Knowledge of the genes associated with IQ has increased. A publicly available database explores IQ-associated human genes [7], revealing that IQ-associated genes are significantly enriched in multiple signaling events, especially those related to cognitive systems.

Several previous reports suggested that IQ can affect and also be affected by addictive behaviors or the use of addictive substances. For example, people with lower IQ scores are more likely to become cigarette smokers [8,9]. In a longitudinal study that assessed marijuana's impact on IQ, current marijuana use was found to be significantly and dose-dependently correlated ($p < 0.05$) with a decline in IQ over the ages studied [10]. High childhood IQ has generally been linked to alcohol dependence and more frequent alcohol consumption [11,12]. In a study that investigated demographic profiles related to estimations

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Received January 30, 2014; Accepted March 29, 2014; Published March 31, 2014


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of Wechsler Adult Intelligence Scale-Revised (WAIS-R) Full Scale IQs (DP Estimated IQs), the DP Estimated IQ was found to be significantly related to the duration of opioid addiction, and a higher estimated IQ was associated with a shorter duration [13]. However, few studies have focused on genes or their functional involvement in the mechanism of addiction in the context of investigating genes related to human intelligence or IQ scores.

To explore the genetic factors that contribute to IQ, we conducted an association study of a genetic polymorphism, rs2952768. The potent rs2952768 single-nucleotide polymorphism (SNP) was recently associated with human opioid sensitivity and shown to be associated with the efficacy of opioid analgesics, severity of substance dependence, and mRNA expression levels of a neighboring gene, CREB1 [14].

Materials and Methods

Subjects

The data from 298 healthy subjects (40.9% male [122/176]; mean age ± SD: 36.8 ± 12.4 years) were used in the present study. The subjects were all biologically unrelated and Japanese. The subjects were recruited through local advertisements at Osaka University. Psychiatrically, medically, and neurologically healthy subjects were evaluated using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), Non-Patient Edition (SCID-I/NP), to exclude individuals who had substance-related disorders, who had received psychiatric medications, or who had first- or second-degree relatives with psychiatric disorders. Additionally, subjects were excluded from the study if they had neurological or medical conditions that could potentially affect their central nervous system, such as atypical headaches, head trauma with loss of consciousness, chronic lung disease, kidney disease, chronic hepatic disease, thyroid disease, active cancer, cerebrovascular disease, epilepsy, seizures, or mental retardation. Written informed consent was obtained from all of the subjects after the procedures were explained. This study was performed in accordance with the World Medical Association’s Declaration of Helsinki and approved by the Osaka University Research Ethics Committee.

Measurement of intellectual ability

Current low IQ may or may not be a determinant of drug and alcohol dependence or the use of addictive substances, and the tendency toward an association may be different between abused substances [8-13]. Based on our evidence that a genetic variant close to the methyltransferase like 21A (METTL21A) gene, rs2952768, is related to the severity of drug and alcohol dependence, we investigated the association between the rs2952768 genotype for drug and alcohol dependence and current IQ in healthy Japanese subjects. To assess current intellectual ability, we used verbal IQ from the Japanese version of the Wechsler Adult Intelligence Scale-Revised (WAIS-III) [15]. The subjects were assessed by trained clinical psychologists to obtain verbal IQ scores on the WAIS-III.

Single-nucleotide polymorphism genotyping

Venous blood was collected from the subjects, and genomic DNA was extracted from whole blood according to standard procedures. Genotyping was performed using the Affymetrix Genome-Wide Human SNP Array 6.0 (Affymetrix, Santa Clara, CA, USA) as previously described [16]. The rs2952768 SNP close to the METTL21A gene was extracted from this dataset. No deviation from Hardy-Weinberg equilibrium (HWE) in the examined SNP was detected (p = 0.10).

Statistical analysis

Differences in clinical characteristics between the genotype groups were analyzed using the χ² tests for categorical variables and Kruskal-Wallis test for continuous variables using PASW Statistics 18.0 software (SPSS Japan, Tokyo, Japan). Deviation from HWE was tested using the χ² test for goodness-of-fit using SNPAlyze 5.1.1 Pro software (DYNACOM, Yokohama, Japan). Multiple linear regression analysis was performed to compare intellectual ability among rs2952768 SNP genotypes (the number of major alleles: 0, 1, or 2) using PASW software. Intellectual ability may be influenced by sex and years of education, and these variables were corrected for as covariates. We did not include age as a covariate because IQ score was already corrected for age. All p values were two tailed, and statistical significance was defined as p < 0.05.

Results

Influence of the rs2952768 genotype on current intellectual ability

Demographic variables, mean age, sex, and years of education are shown in Table 1. The mean age and years of education did not differ significantly between the genotype groups (p > 0.59), whereas the sex ratio differed significantly between groups (p = 0.015). We examined the possible effect of the rs2952768 genotype on intellectual ability. A significant effect of the SNP genotype was observed on current IQ (β = -2.27, p = 0.026). The number of C allele was correlated with higher IQ scores (Figure 1).

Table 1: Demographic variables for subjects included in this study.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total (N = 298)</th>
<th>C/C (N = 123)</th>
<th>T/C (N = 122)</th>
<th>T/T (N = 122)</th>
<th>p (H)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>36.8 ± 12.4</td>
<td>36.3 ± 13.6</td>
<td>37.0 ± 11.7</td>
<td>36.8 ± 12.6</td>
<td>0.83 (0.38)</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>122/176</td>
<td>11/34</td>
<td>60/83</td>
<td>51/79</td>
<td>0.015 (0.35F)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>14.9 ± 2.3</td>
<td>15.0 ± 2.3</td>
<td>14.8 ± 2.3</td>
<td>15.0 ± 2.3</td>
<td>0.59 (1.06)</td>
</tr>
</tbody>
</table>

Means ± SD are shown, p < 0.05 is in boldface and underlined χ² test.

Figure 1: Impact of the rs2952768 genotype on intellectual ability

While, gray, and black bars represent individuals with the C/C genotype, T/C genotype, and T/T genotype, respectively. Error bars represent the standard error. The asterisk indicates p<0.05.
Discussion

We conducted an association study between verbal IQ and the rs2952768 SNP, which was recently identified as a potent SNP associated with opioid sensitivity that affects both the efficacy of opioid analgesics and liability to severe substance dependence. A significant effect of the SNP genotype was observed on current IQ ($\beta = -2.27, p = 0.026$), and the number of non-risk major C allele for severe drug and alcohol dependence was correlated with higher IQ scores (Figure 1), suggesting that the rs2952768 SNP is one of the genetic factors that contribute to human intellectual ability.

Several previous reports suggested associations between IQ score and addictive behaviors or the use of addictive substances, but the trend toward an association is not straightforward or easily understood [8-13]. Several reports indicated that people with lower IQ scores are more likely to become cigarette smokers [8,9]. Another report found that higher estimated IQ was significantly related to a shorter duration of opioid addiction [13]. High childhood IQ generally has been linked with alcohol dependence and more frequent alcohol consumption, and a 1 SD (15-point) increase in IQ score was found to be associated with an increased risk of illegal drug use in women, such as the use of cannabis, cocaine, amphetamines, amyl nitrate, and “magic mushrooms” [11,12]. The outcome in the present study that the number of non-risk major C allele for substance dependence in the rs2952768 SNP was correlated with higher IQ scores (Figure 1) is seemingly consistent with the results reported by Chastain et al. [13]. Although the rs2952768 SNP was identified as an opioid sensitivity-related SNP, the association was also found in the same direction with the severity of substance dependence, including alcohol dependence, methamphetamine dependence, and eating disorder [14]. Much more studies will be required to make definitive conclusions about the correlations or causal associations between IQ and the use of various addictive substances and vulnerability to or severity of dependence, since the fundamentally important pre-condition, the relationship of rs2952768 with severe drug dependence, has not been well-established.

In our previous study, the homozygote of the non-risk C allele for severe drug and alcohol dependence of the rs2952768 SNP was significantly associated with the elevated expression of a neighboring gene, cyclic adenosine monophosphate response element binding protein 1 (*CREB1*), which encodes a transcription factor that is a member of the leucine zipper family of DNA binding proteins. CREB plays various roles as a transcription factor in many cells, including neuronal cells, and it is also involved in the molecular mechanisms that couple synaptic activity to long-term changes in neuronal plasticity, which is thought to underlie learning and memory [17]. Therefore, the elevated expression of the *CREB1* gene may promote the transcription levels of some target genes related to both human intellectual ability and addiction, leading to alterations in the neural mechanisms that are involved in both increasing intelligence and decreasing the rewarding effects of addictive substances. However, such speculative statements should be avoided before much more extensive studies are conducted in the future, and the precise mechanism by which elevated *CREB1* expression generally affects human opioid sensitivity requires further study.

The *CREB1* and *METTL21A* genes are both located within a linkage disequilibrium block that spans 2q33.3–2q34 [14]. Although these genes were not contained in the publicly available database that explores IQ-associated human genes [7], the chromosomal region 2q33 was included in the linkage regions, indicating that this region may be an IQ-associated region. Furthermore, chromosomal abnormalities, such as duplication and deletion of 2q33.3–2q34, were reported in patients with developmental delay and mental retardation [18,19], the severity of which may be related to IQ [20]. Despite the fact that the responsible genes within this region for IQ should be further clarified in future studies, these previous reports support the results of the present study, in which SNPs in this region may be associated with intellectual ability.

In conclusion, we identified a significant effect of the SNP genotype on current IQ, and the number of non-risk major C allele for drug and alcohol dependence was correlated with higher IQ scores. Although we should not over-interpret the present finding and the precise underlying mechanisms remain to be clarified in future studies, the results of the present study suggest that this SNP may be one of the genetic factors that contribute to human intellectual ability.

Acknowledgements

We acknowledge Mr. Michael Arends for his assistance with editing the manuscript. We thank all of the individuals who participated in this study. This work was supported by research grants from the Ministry of Health, Labour and Welfare (MHLW) of Japan (H22-seishin-ippan-001 and H25-lyaku-020), JEXT/JSPS KAKENHI (grant no. 22390225, 23659955, 21156232, 20602020, 20390162, 23390377, 24790544, 24659549, and 22790518), CREST of JST, Japan Foundation for Neuroscience and Mental Health, and Smoking Research Foundation.

References


